Clinical trial results:
A Phase 4 Safety and Efficacy Study of Bosutinib (Bosulif®) in Subjects With Philadelphia Chromosome Positive Chronic Myeloid Leukemia Previously Treated With one or More Tyrosine Kinase Inhibitors

Summary

EudraCT number	2013-003250-25
Trial protocol	SE FI DE IT BE NL ES AT NO
Global end of trial date	13 October 2020

Results information

Result version number	v1 (current)
This version publication date	28 October 2021
First version publication date	28 October 2021

Trial information

Trial identification

Sponsor protocol code	B1871039

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02228382
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2020
Global end of trial reached?	Yes
Global end of trial date	13 October 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To estimate the 1-year (52-week) probability of cumulative confirmed major cytogenetic response (MCyR) in chronic phase (CP) philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia (CML) subjects with 1 or 2 prior lines of tyrosine kinase inhibitors (TKI) therapy.
To estimate the 1-year (52-week) probability of cumulative confirmed MCyR in CP Ph+ CML subjects with 3 or more prior lines of TKI therapy.
To estimate the 1-year (52-week) probability of cumulative confirmed overall hematological response (OHR) in AP and BP Ph+ CML subjects with any prior TKI therapy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 November 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Italy: 42
Country: Number of subjects enrolled	Norway: 11
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	United States: 38
Worldwide total number of subjects	163
EEA total number of subjects	125

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	101
From 65 to 84 years	56
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Subjects with chronic phase (CP), accelerated P (AP), or blast P (BP) philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML), or with breakpoint cluster region-abelson kinase(BCR-ABL1)+ and Philadelphia chromosome negative(Ph-), who failed prior treatment with commercially available tyrosine kinase inhibitors(TKIs) were enrolled.

Pre-assignment

Screening details:

A total of 177 subjects signed the inform consent form (ICF), 14 subjects were screen failure and 163 were enrolled into the study and assigned to study treatment. Total 163 subjects were enrolled at 48 sites in 8 countries. Study started from 07-Nov-2014 and completed on 13-Oct-2020. No subjects with BP were enrolled in the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Bosutinib: Chronic Phase 2nd Line CML

Arm description:

Subjects with philadelphia chromosome positive chronic phase 2nd line chronic myelogenous leukemia resistant or intolerant to imatinib, dasatinib, or nilotinib received bosutinib 500 milligram (mg), orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Arm type	Experimental
Investigational medicinal product name	Bosutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bosutinib 500 milligrams (mg) once daily.

Arm title	Bosutinib: Chronic Phase 3rd Line CML

Arm description:

Subjects with philadelphia chromosome positive chronic Phase 3rd line chronic myelogenous leukemia resistant or intolerant to imatinib and/or dasatinib and/or nilotinib received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Arm type	Experimental
Investigational medicinal product name	Bosutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bosutinib 500 mg once daily.

Arm title	Bosutinib: Chronic Phase 4th Line CML

Arm description:

Subjects with philadelphia chromosome positive chronic phase 4th line chronic myelogenous leukemia resistant or intolerant to imatinib and dasatinib and nilotinib received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Arm type	Experimental
Investigational medicinal product name	Bosutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bosutinib 500 mg once daily.

Arm title	Bosutinib: Accelerated Phase CML

Arm description:

Subjects with philadelphia chromosome positive accelerated phase chronic myelogenous leukemia resistant or intolerant to at least one tyrosine kinase inhibitor among imatinib, dasatinib, or nilotinib received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Arm type	Experimental
Investigational medicinal product name	Bosutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bosutinib 500 mg once daily.

Arm title	Bosutinib: Philadelphia Chromosome Negative CML

Arm description:

Subjects with BCR-ABL1 positive and philadelphia chromosome negative chronic myelogenous leukemia received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Arm type	Experimental
Investigational medicinal product name	Bosutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bosutinib 500 mg once daily.

Number of subjects in period 1	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML
Started	46	61	49
Completed	36	43	28
Not completed	10	18	21
Consent withdrawn by subject	-	3	2
Study terminated by sponsor	3	5	7
Subject died	5	7	5
Unspecified	2	3	3
Subject refused further follow-up	-	-	1
Lost to follow-up	-	-	3

Number of subjects in period 1	Bosutinib: Accelerated Phase CML	Bosutinib: Philadelphia Chromosome Negative CML
Started	4	3
Completed	2	1
Not completed	2	2
Consent withdrawn by subject	1	-
Study terminated by sponsor	-	-
Subject died	-	2
Unspecified	-	-
Subject refused further follow-up	-	-
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Bosutinib: Chronic Phase 2nd Line CML

Reporting group description:

Subjects with philadelphia chromosome positive chronic phase 2nd line chronic myelogenous leukemia resistant or intolerant to imatinib, dasatinib, or nilotinib received bosutinib 500 milligram (mg), orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Reporting group title	Bosutinib: Chronic Phase 3rd Line CML

Reporting group description:

Subjects with philadelphia chromosome positive chronic Phase 3rd line chronic myelogenous leukemia resistant or intolerant to imatinib and/or dasatinib and/or nilotinib received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Reporting group title	Bosutinib: Chronic Phase 4th Line CML

Reporting group description:

Subjects with philadelphia chromosome positive chronic phase 4th line chronic myelogenous leukemia resistant or intolerant to imatinib and dasatinib and nilotinib received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Reporting group title	Bosutinib: Accelerated Phase CML

Reporting group description:

Subjects with philadelphia chromosome positive accelerated phase chronic myelogenous leukemia resistant or intolerant to at least one tyrosine kinase inhibitor among imatinib, dasatinib, or nilotinib received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Reporting group title	Bosutinib: Philadelphia Chromosome Negative CML

Reporting group description:

Subjects with BCR-ABL1 positive and philadelphia chromosome negative chronic myelogenous leukemia received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Reporting group values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML
Number of subjects	46	61	49
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	34	30	31

From 65-84 years	9	29	17
85 years and over	3	2	1

Age Continuous			
Units: Years			
arithmetic mean	55.8	61.8	59.4
standard deviation	± 15.4	± 15.0	± 15.3
Sex: Female, Male			
Units: Subjects			
Female	23	24	28
Male	23	37	21
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	1
White	39	55	44
More than one race	0	0	0
Unknown or Not Reported	5	4	4

Reporting group values	Bosutinib: Accelerated Phase CML	Bosutinib: Philadelphia Chromosome Negative CML	Total
Number of subjects	4	3	163
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	2	101
From 65-84 years	0	1	56
85 years and over	0	0	6
Age Continuous			
Units: Years			
arithmetic mean	40.8	64.3	
standard deviation	± 11.0	± 7.1	-
Sex: Female, Male			
Units: Subjects			
Female	0	0	75
Male	4	3	88
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	0	0	4
White	2	3	143
More than one race	0	0	0
Unknown or Not Reported	2	0	15

End points

End points reporting groups

Reporting group title	Bosutinib: Chronic Phase 2nd Line CML

Reporting group description:

Subjects with philadelphia chromosome positive chronic phase 2nd line chronic myelogenous leukemia resistant or intolerant to imatinib, dasatinib, or nilotinib received bosutinib 500 milligram (mg), orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Reporting group title	Bosutinib: Chronic Phase 3rd Line CML

Reporting group description:

Subjects with philadelphia chromosome positive chronic Phase 3rd line chronic myelogenous leukemia resistant or intolerant to imatinib and/or dasatinib and/or nilotinib received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Reporting group title	Bosutinib: Chronic Phase 4th Line CML

Reporting group description:

Subjects with philadelphia chromosome positive chronic phase 4th line chronic myelogenous leukemia resistant or intolerant to imatinib and dasatinib and nilotinib received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Reporting group title	Bosutinib: Accelerated Phase CML

Reporting group description:

Subjects with philadelphia chromosome positive accelerated phase chronic myelogenous leukemia resistant or intolerant to at least one tyrosine kinase inhibitor among imatinib, dasatinib, or nilotinib received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Reporting group title	Bosutinib: Philadelphia Chromosome Negative CML

Reporting group description:

Subjects with BCR-ABL1 positive and philadelphia chromosome negative chronic myelogenous leukemia received bosutinib 500 mg, orally once daily until disease progression, unacceptable toxicity, withdrawal of consent, death or discontinuation of study (up to maximum of 4 years). Subjects who discontinued bosutinib prior to completing at least 4 years of therapy were followed for survival until they completed at least 4 years of follow-up from the time of first dose.

Subject analysis set title	Bosutinib: Chronic Phase 2nd and 3rd Line CML
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with philadelphia chromosome positive chronic phase 2nd and 3rd line chronic myelogenous leukemia.

Subject analysis set title	Bosutinib: Chronic Myelogenous Leukemia
Subject analysis set type	Safety analysis

Subject analysis set description:

Subjects with philadelphia chromosome positive chronic phase 2nd, 3rd and 4th line CML, philadelphia chromosome positive accelerated phase CML and BCR-ABL1-positive/philadelphia chromosome negative CML.

Primary: Percentage of Subjects With Cumulative Confirmed Major Cytogenetic Response (MCyR) in 2nd and 3rd Line Chronic Phase (CP) Subjects

End point title	Percentage of Subjects With Cumulative Confirmed Major Cytogenetic Response (MCyR) in 2nd and 3rd Line Chronic Phase (CP) Subjects[1]

End point description:

Confirmed MCyR: confirmed CCyR or PCyR by 1 year for subjects entering the study without CCyR or maintenance of confirmed CCyR for at least 1 year after treatment start with bosutinib for subjects entering the study with CCyR or at least MMR by 1 year and a deeper molecular response compared to baseline. Subjects with baseline PCyR that did not achieve CCyR were counted as nonresponders. Initial cytogenetic (in absence of MMR) responses must have been confirmed by 2 consecutive assessments >=28 days apart. CCyR: 0% Ph+ cells from >=20 metaphases from conventional cytogenetics or <1% Ph+ cells from >= 200 cells from fluorescent in situ hybridization(FISH). PCyR: 1 to 35% Ph+ cells. MMR: <=0.1% BCR-ABL1 on the international scale (IS) with at least 10,000 ABL1 transcripts assessed by central laboratory. Evaluable set cytogenetic response:treated subjects with valid baseline efficacy assessment(>=20 metaphases from baseline bone marrow/CCyR with >=200 cells from FISH/baseline MMR).

End point type	Primary

End point timeframe:

Up to 1 year (52 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was done for this endpoint.

End point values	Bosutinib: Chronic Phase 2nd and 3rd Line CML			
Subject group type	Subject analysis set			
Number of subjects analysed	98			
Units: percentage of subjects				
number (confidence interval 95%)	76.5 (66.9 to 84.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Cumulative Confirmed Major Cytogenetic Response (MCyR) in 4th or Later Line Chronic Phase (CP) Subjects

End point title	Percentage of Subjects With Cumulative Confirmed Major Cytogenetic Response (MCyR) in 4th or Later Line Chronic Phase (CP) Subjects[2][3]

End point description:

Confirmed MCyR: confirmed CCyR or PCyR by 1 year for subjects entering the study without CCyR or maintenance of confirmed CCyR for at least 1 year after treatment start with bosutinib for subjects entering the study with CCyR or at least MMR by 1 year and a deeper molecular response compared to baseline. Subjects with baseline PCyR that did not achieve CCyR were counted as nonresponders. Initial cytogenetic (in absence of MMR) responses must have been confirmed by 2 consecutive assessments >=28 days apart. CCyR: 0% Ph+ cells from >=20 metaphases from conventional cytogenetics or <1% Ph+ cells from >= 200 cells from FISH. PCyR: 1 to 35% Ph+ cells. MMR: <=0.1% BCR-ABL1 on the IS with at least 10,000 ABL1 transcripts assessed by central laboratory. Evaluable set cytogenetic response:treated subjects with valid baseline efficacy assessment(>=20 metaphases from baseline bone marrow/CCyR with >=200 cells from FISH/baseline MMR).

End point type	Primary

End point timeframe:

Up to 1 year (52 weeks)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was done for this endpoint.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only for the arms specified.

End point values	Bosutinib: Chronic Phase 4th Line CML			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: percentage of subjects				
number (confidence interval 95%)	62.2 (46.5 to 76.2)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Cumulative Confirmed Overall Heamatological Response (OHR) in Accelerated Phase (AP) Chronic Myelogenous Leukemia (CML) Subjects

End point title	Percentage of Subjects With Cumulative Confirmed Overall Heamatological Response (OHR) in Accelerated Phase (AP) Chronic Myelogenous Leukemia (CML) Subjects[4][5]

End point description:

Confirmed OHR was defined as complete hematological response (CHR) or return to chronic phase (RCP) by 1 year in AP and BP subjects. CHR was defined as white blood cells (WBC) <10*10^9/L, peripheral blood basophils <5%, no peripheral blood myelocytes, promyelocytes, myeloblasts in the differential, platelet count <450*10^9/L, spleen not palpable. Hematologic responses must be of >=4 weeks duration confirmed by 2 assessments >=4 weeks apart. Evaluable set for hematological response: treated subjects with a valid baseline hematologic assessment. Data for this endpoint was not planned to be collected and analysed for CP2L, CP3L, CP4L and Ph- CML subjects.

End point type	Primary

End point timeframe:

Up to 1 year (52 weeks)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was done for this endpoint.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only for the arms specified.

End point values	Bosutinib: Accelerated Phase CML			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: percentage of subjects				
number (confidence interval 95%)	75.0 (19.4 to			

	99.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Cumulative Major Cytogenetic Response (MCyR)

End point title	Percentage of Subjects With Cumulative Major Cytogenetic Response (MCyR)[6]

End point description:

CyR was based on prevalence of Ph+ cells. CCyR was achieved when there was 0 % Ph+ cells from >=20 metaphases from conventional bone marrow cytogenetics or <1% Ph+ cells from >=200 cells analysed from FISH. PCyR was achieved when 1 to 35% Ph+ cells were present. MCyR was categorised as either complete cytogenetic response (CCyR) or partial cytogenetic response (PCyR). Subjects with MMR or better at baseline were counted as CCyR if baseline response was maintained or improved while on treatment. Evaluable set cytogenetic response: treated subjects with valid baseline efficacy assessment (>=20 metaphases from baseline bone marrow or CCyR with >=200 cells from FISH or baseline MMR). Data for this endpoint was not planned to be collected and analysed for Ph- subjects.

End point type	Secondary

End point timeframe:

Up to 4 years

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was analyzed only for the arms specified.

End point values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML	Bosutinib: Accelerated Phase CML
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	55	45	4
Units: percentage of subjects				
number (confidence interval 95%)	88.4 (74.9 to 96.1)	85.5 (73.3 to 93.5)	77.8 (62.9 to 88.8)	75.0 (19.4 to 99.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Cumulative Confirmed Overall Heamatological Response (OHR) in Subjects With Accelerated Phase (AP) Chronic Myelogenous Leukemia (CML)

End point title	Percentage of Subjects With Cumulative Confirmed Overall Heamatological Response (OHR) in Subjects With Accelerated Phase (AP) Chronic Myelogenous Leukemia (CML)[7]

End point description:

Confirmed OHR was defined as CHR or RCP in AP and BP subjects. CHR was defined as WBC <10*10^9/L, peripheral blood basophils <5%, no peripheral blood myelocytes, promyelocytes, myeloblasts in the differential, platelet count <450*10^9/L, spleen not palpable. Hematologic responses

must be of >=4 weeks duration confirmed by 2 assessments >=4 weeks apart. Evaluable set for hematological response: treated subjects with a valid baseline hematologic assessment. Data for this endpoint was not planned to be collected and analysed for CP2L, CP3L, CP4L and Ph- CML subjects.

End point type	Secondary

End point timeframe:

Up to 4 years

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only for the arms specified.

End point values	Bosutinib: Accelerated Phase CML			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: percentage of subjects				
number (confidence interval 95%)	75.0 (19.4 to 99.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Cumulative Best Response

End point title	Percentage of Subjects With Cumulative Best Response[8]

End point description:

Hierarchy best response:%subjects with best response among molecular/cytogenetic/hematologic response. Molecular response:MR4.5/MR4/MMR defined as <=0.0032/0.01/0.1% BCR-ABL1 ratio on IS corresponding to >=4.5/4/3-log reduction from standardised baseline with at least 32000/10000/10000 ABL1 assessed by central laboratory. CyR:based on prevalence of Ph+cells. CCyR: 0% Ph+cells from >=20 metaphases from conventional cytogenetics or <1%Ph+cells from >=200 cells from FISH. PCyR:1 to 35% Ph+cells. CHR:WBC <10*10^9/L, peripheral blood basophils<5%, no peripheral blood myelocytes, promyelocytes, myeloblasts in differential, platelet count<450*10^9/L, spleen not palpable. Evaluable set:treated subjects with valid baseline molecular/cytogenetic/hematologic assessment. Data for this endpoint(all categories including OHR) was not planned to be collected and analysed for Ph- CML subjects. Data for OHR was not planned to be collected and analysed for CP CML subjects.

End point type	Secondary

End point timeframe:

Up to 4 years

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only for the arms specified.

End point values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML	Bosutinib: Accelerated Phase CML
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	61	49	4
Units: percentage of subjects				
number (confidence interval 95%)				
MR4.5	17.4 (7.8 to 31.4)	14.8 (7.0 to 26.2)	8.2 (2.3 to 19.6)	25.0 (0.6 to 80.6)

MR4	15.2 (6.3 to 28.9)	11.5 (4.7 to 22.2)	6.1 (1.3 to 16.9)	0.0 (0.0 to 60.2)
MMR	8.7 (2.4 to 20.8)	11.5 (4.7 to 22.2)	14.3 (5.9 to 27.2)	25.0 (0.6 to 80.6)
CCyR	2.2 (0.1 to 11.5)	13.1 (5.8 to 24.2)	14.3 (5.9 to 27.2)	25.0 (0.6 to 80.6)
PCyR	2.2 (0.1 to 11.5)	1.6 (0.0 to 8.8)	4.1 (0.5 to 14.0)	0.0 (0.0 to 60.2)
CHR	10.9 (3.6 to 23.6)	8.2 (2.7 to 18.1)	16.3 (7.3 to 29.7)	0.0 (0.0 to 60.2)
OHR	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	0.0 (0.0 to 60.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Major Cytogenetic Response (MCyR) at Months 3, 6, 12, 18 and 24

End point title	Percentage of Subjects With Major Cytogenetic Response (MCyR) at Months 3, 6, 12, 18 and 24[9]

End point description:

CyR was based on prevalence of Ph+ cells. CCyR was achieved when there was 0% Ph+ cells from >=20 metaphases from conventional bone marrow cytogenetics or <1% Ph+ cells from >=200 cells analysed from FISH. PCyR was achieved when 1 to 35% Ph+ cells were present. MCyR was categorised as either CCyR or PCyR. Subjects with MMR or better at baseline were counted as CCyR if baseline response was maintained or improved while on treatment. Evaluable set cytogenetic response: treated subjects with valid baseline efficacy assessment (>=20 metaphases from baseline bone marrow or CCyR with >=200 cells from FISH or baseline MMR). Data for this endpoint was not planned to be collected and analysed for Ph- subjects.

End point type	Secondary

End point timeframe:

Months 3, 6, 12, 18, and 24

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only for the arms specified.

End point values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML	Bosutinib: Accelerated Phase CML
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	55	45	4
Units: percentage of subjects				
number (confidence interval 95%)				
At 3 months	81.4 (66.6 to 91.6)	80.0 (67.0 to 89.6)	55.6 (40.0 to 70.4)	75.0 (19.4 to 99.4)
At 6 months	69.8 (53.9 to 82.8)	63.6 (49.6 to 76.2)	62.2 (46.5 to 76.2)	25.0 (0.6 to 80.6)
At 12 months	69.8 (53.9 to 82.8)	65.5 (51.4 to 77.8)	48.9 (33.7 to 64.2)	25.0 (0.6 to 80.6)
At 18 months	67.4 (51.5 to 80.9)	63.6 (49.6 to 76.2)	42.2 (27.7 to 57.8)	25.0 (0.6 to 80.6)
At 24 months	67.4 (51.5 to 80.9)	54.5 (40.6 to 68.0)	44.4 (29.6 to 60.0)	25.0 (0.6 to 80.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Accelerated Phase Subjects With Confirmed Overall Hematological Response (OHR) at Month 3, 6, 9, 12, 18, and 24

End point title	Percentage of Accelerated Phase Subjects With Confirmed Overall Hematological Response (OHR) at Month 3, 6, 9, 12, 18, and 24[10]

End point description:

Confirmed OHR was defined as CHR or RCP in AP and BP subjects. CHR was defined as WBC <10*10^9/L, peripheral blood basophils <5%, no peripheral blood myelocytes, promyelocytes, myeloblasts in the differential, platelet count <450*10^9/L, spleen not palpable. Hematologic responses must be of >=4 weeks duration confirmed by 2 assessments >=4 weeks apart. Evaluable set hematological response: treated subjects with a valid baseline hematologic assessment. Data for this endpoint was not planned to be collected and analysed for CP2L, CP3L, CP4L and Ph- CML subjects.

End point type	Secondary

End point timeframe:

Months 3, 6, 9, 12, 18, and 24

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only for the arms specified.

End point values	Bosutinib: Accelerated Phase CML			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: percentage of subjects				
number (confidence interval 95%)				
At 3 months	75.0 (19.4 to 99.4)			
At 6 months	50.0 (6.8 to 93.2)			
At 9 months	75.0 (19.4 to 99.4)			
At 12 months	75.0 (19.4 to 99.4)			
At 18 months	25.0 (0.6 to 80.6)			
At 24 months	0.0 (0.0 to 60.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Cumulative Confirmed Complete Hematological Response (CHR)

End point title	Percentage of Subjects With Cumulative Confirmed Complete Hematological Response (CHR)[11]

End point description:

CHR was defined as WBC <10*10^9/L, peripheral blood basophils <5%, no peripheral blood myelocytes, promyelocytes, myeloblasts in the differential, platelet count <450*10^9/L, spleen not palpable. Hematologic responses must be of >=4 weeks duration confirmed by 2 assessments >=4 weeks apart. Evaluable set for hematological response: treated subjects with a valid baseline hematologic assessment. Data for this endpoint was not planned to be collected and analysed for Ph- subjects.

End point type	Secondary

End point timeframe:

Up to 4 years

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only for the arms specified.

End point values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML	Bosutinib: Accelerated Phase CML
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	61	48	4
Units: percentage of subjects				
number (confidence interval 95%)	91.3 (79.2 to 97.6)	82.0 (70.0 to 90.6)	77.1 (62.7 to 88.0)	75.0 (19.4 to 99.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Cumulative Major Molecular Response (MMR)

End point title	Percentage of Subjects With Cumulative Major Molecular Response (MMR)[12]

End point description:

Molecular response: MR4.5/MR4/MMR defined as <=0.0032/0.01/0.1% BCR-ABL1 ratio respectively, on IS corresponding to >=4.5/4/3-log reduction from standardized baseline with at least 32000/10000/10000 ABL1 assessed by central laboratory. To be considered a responder, the subject must have had maintenance of baseline response while on-treatment or an improvement from baseline. Evaluable set molecular response: treated subjects with a valid baseline molecular assessment from central lab. Data for this endpoint was not planned to be collected and analysed for Ph- subjects.

End point type	Secondary

End point timeframe:

Up to 4 years

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only for the arms specified.

End point values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML	Bosutinib: Accelerated Phase CML
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	55	48	4
Units: percentage of subjects				
number (confidence interval 95%)				
MMR	82.6 (68.6 to 92.2)	76.4 (63.0 to 86.8)	56.3 (41.2 to 70.5)	50.0 (6.8 to 93.2)
MR4	73.9 (58.9 to 85.7)	63.6 (49.6 to 76.2)	41.7 (27.6 to 56.8)	25.0 (0.6 to 80.6)
MR4.5	58.7 (43.2 to 73.0)	50.9 (37.1 to 64.6)	35.4 (22.2 to 50.5)	25.0 (0.6 to 80.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Probability of Retaining Complete Cytogenetic Response (CCyR) at Month 36

End point title	Kaplan-Meier Estimate of Probability of Retaining Complete Cytogenetic Response (CCyR) at Month 36[13]

End point description:

Kaplan-Meier analysis. Duration CCyR:from first date of CCyR to date of confirmed loss of CCyR/disease progression/on-treatment death or censoring,analyzed for responders only.CyR:prevalence of Ph+cells. CCyR:0%Ph+cells from>=20metaphases from conventional cytogenetics or <1%Ph+cells from>=200 cells analyzed by FISH/MMR(<=0.1%BCR-ABL1 onIS with atleast 10,000ABL1 transcripts assessed by central laboratory). Confirmed loss:2 consecutive non-response assessments >=28days apart. Progression:forCP: subjects evolving from CP to AP,loss of CHR;loss of MCyR;in subjects without CHR WBC>20*10^9/L on occasions >=2 weeks apart after first 4 weeks of treatment;for AP:confirmed BP,loss of previous hematologic response over 2week period,loss of CHR, no decrease from baseline levels(if considered clinically relevant)in percentage blasts in peripheral blood/bone marrow on all assessments over 4week period. Evaluable set:treated subjects with valid baselinecytogenetic assessmentandwho achieved CCyR.

End point type	Secondary

End point timeframe:

At Month 36

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only for the arms specified.

End point values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML	Bosutinib: Accelerated Phase CML
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	37	46	33	3
Units: percentage of subjects				
number (confidence interval 95%)	96.4 (77.2 to 99.5)	94.4 (79.2 to 98.6)	100.0 (100.0 to 100.0)	100.0 (100.0 to 100.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Probability of Retaining Major Molecular Response (MMR) at Month 36

End point title	Kaplan-Meier Estimate of Probability of Retaining Major Molecular Response (MMR) at Month 36[14]

End point description:

Kaplan-Meier analysis. Duration of MMR: from first date of MMR to confirmed loss of MMR/disease progression/on-treatment death or censoring, analyzed for responders only. MMR:<=0.1%BCR-ABL1 on the IS with atleast 10,000 ABL1 transcripts assessed by central laboratory . Confirmed loss: 2 consecutive non-response assessments >=28 days apart with a <3-log (>0.1%) reduction in transcripts one of which corresponds to a <=2-log reduction (>=1%). Progression: for CP: subject evolving from CP to AP, loss of CHR; loss of MCyR; in subjects without CHR WBC >20*10^9/L on 2 occasions >=2weeks apart after the first 4 weeks of treatment; for AP: confirmed BP, loss of previous hematologic response over a 2-week period, loss of CHR, no decrease from baseline levels (if considered clinically relevant) in percentage blasts in peripheral blood or bone marrow on all assessments over a 4-week period. Evaluable set: treated subjects with valid baseline molecular assessment and who achieved MMR.

End point type	Secondary

End point timeframe:

At Month 36

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was analyzed only for the arms specified.

End point values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML	Bosutinib: Accelerated Phase CML
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	42	27	2
Units: percentage of subjects				
number (confidence interval 95%)	90.7 (73.9 to 96.9)	81.5 (63.2 to 91.3)	90.2 (65.9 to 97.5)	100.0 (100.0 to 100.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious AEs

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious AEs

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. TEAE: any event increasing in severity from baseline or any new event started during bosutinib therapy or within 28 days of the last dose of study drug. SAE: an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial/prolonged inpatient hospitalization; life-threatening experience (immediate risk of death); persistent or significant disability/incapacity; congenital anomaly. The safety analysis set included subjects who received at least 1 dose of bosutinib.

End point type	Secondary

End point timeframe:

First dose of study drug up to 28 days after last dose (up to maximum of 4 years)

End point values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML	Bosutinib: Accelerated Phase CML
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	61	49	4
Units: subjects				
TEAEs	46	61	48	4
Treatment-emergent SAEs	21	30	14	1

End point values	Bosutinib: Philadelphia Chromosome Negative CML	Bosutinib: Chronic Myelogenous Leukemia		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	163		
Units: subjects				
TEAEs	3	162		
Treatment-emergent SAEs	3	69		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 3 or 4 Treatment Emergent Adverse Events (TEAEs) Based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

End point title	Number of Subjects With Grade 3 or 4 Treatment Emergent Adverse Events (TEAEs) Based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. TEAE was any event increasing in severity from baseline or any new event that started during bosutinib therapy or within 28 days of the last dose of study drug. Severity was graded as Grade 1: asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; Grade 2: moderate, minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily life (ADL); Grade 3: severe or medically significant but not immediately life-threatening, hospitalization or prolongation of existing hospitalization indicated, disabling, limiting self-care ADL; Grade 4: life-threatening consequence, urgent intervention indicated; Grade 5: death related to AE. Number of subjects with Grade 3 or 4 TEAEs are reported. The saftey analysis set included subjects who received at least 1 dose of bosutinib.

End point type	Secondary

End point timeframe:

First dose of study drug up to 28 days after last dose (up to maximum of 4 years)

End point values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML	Bosutinib: Accelerated Phase CML
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	61	49	4
Units: subjects	36	49	39	2

End point values	Bosutinib: Philadelphia Chromosome Negative CML	Bosutinib: Chronic Myelogenous Leukemia		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	163		
Units: subjects	3	129		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Related Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment Related Treatment Emergent Adverse Events (TEAEs)

End point description:

An AE was any untoward medical occurrence attributed to study drug in a subject who received study drug. TEAE was any event increasing in severity from baseline or any new event that started during bosutinib therapy or within 28 days of the last dose of study drug. Relatedness to drug was assessed by investigator. The safety analysis set included subjects who received at least 1 dose of bosutinib.

End point type	Secondary

End point timeframe:

First dose of study drug up to 28 days after last dose (up to maximum of 4 years)

End point values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML	Bosutinib: Accelerated Phase CML
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	61	49	4
Units: subject	46	61	48	4

End point values	Bosutinib: Philadelphia	Bosutinib: Chronic		

	Chromosome Negative CML	Myelogenous Leukemia		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	162		
Units: subject	3	162		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Abnormalities Based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

End point title	Number of Subjects With Laboratory Abnormalities Based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

End point description:

Haematological: absolute neutrophil count (low), haemoglobin (low), lymphocytes (low), platelets (low) and leukocytes (low). Chemistry: alkaline phosphatase (high), alanine aminotransferase (high), amylase (high), aspartate aminotransferase (high), bilirubin (high), creatinine (high), lipase (high). Coagulation: activated partial prothrombin time (low), prothrombin time (low and high), partial prothrombin time (high). Number of subjects with any haematological, chemistry and coagulation abnormality of any grade were reported. The safety analysis set included subjects who received at least 1 dose of bosutinib.

End point type	Secondary

End point timeframe:

First dose of study drug up to 28 days after last dose (up to maximum of 4 years)

End point values	Bosutinib: Chronic Phase 2nd Line CML	Bosutinib: Chronic Phase 3rd Line CML	Bosutinib: Chronic Phase 4th Line CML	Bosutinib: Accelerated Phase CML
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	61	49	4
Units: subjects				
Hematology	38	56	40	4
Chemistry	46	61	49	4
Coagulation	18	25	12	2

End point values	Bosutinib: Philadelphia Chromosome Negative CML	Bosutinib: Chronic Myelogenous Leukemia		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3	163		
Units: subjects				
Hematology	3	141		
Chemistry	3	163		
Coagulation	1	58		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 28 days after last dose (up to maximum of 4 years)

Adverse event reporting additional description:

The total number of deaths occurring during study, from first dose and up to the end of the study are reported for all treated subjects and includes deaths which occurred after 28 days post last study drug dose. An event may be serious in one subject and non-serious in another/a subject may have experienced both a serious and non-serious event.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Bosutinib, Chronic Phase 2nd Line CML

Reporting group description:

Subjects with philadelphia chromosome positive chronic phase 2nd line chronic myelogenous leukemia.

Reporting group title	Bosutinib, Chronic Phase 3rd Line CML

Reporting group description:

Subjects with philadelphia chromosome positive chronic phase 3rd line chronic myelogenous leukemia.

Reporting group title	Bosutinib, Chronic Phase 4th Line CML

Reporting group description:

Subjects with philadelphia chromosome positive chronic phase 4th line chronic myelogenous leukemia.

Reporting group title	Bosutinib, Accelerated Phase CML

Reporting group description:

Subjects with philadelphia chromosome positive accelerated phase line chronic myelogenous leukemia.

Reporting group title	Bosutinib, Philadelphia Chromosome Negative CML

Reporting group description:

Subjects with philadelphia chromosome negative chronic myelogenous leukemia.

Reporting group title	Bosutinib: Chronic Myelogenous Leukemia

Reporting group description:

Subjects with philadelphia chromosome positive chronic phase 2nd, 3rd and 4th line CML, philadelphia chromosome positive accelerated phase CML and BCR-ABL1-positive/philadelphia chromosome negative CML.

Serious adverse events	Bosutinib, Chronic Phase 2nd Line CML	Bosutinib, Chronic Phase 3rd Line CML	Bosutinib, Chronic Phase 4th Line CML
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 46 (45.65%)	30 / 61 (49.18%)	14 / 49 (28.57%)
number of deaths (all causes)	5	7	5
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			

subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaplastic large-cell lymphoma			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Brain neoplasm			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 46 (0.00%)	2 / 61 (3.28%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 46 (0.00%)	2 / 61 (3.28%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 46 (2.17%)	3 / 61 (4.92%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst ruptured			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 46 (4.35%)	1 / 61 (1.64%)	3 / 49 (6.12%)
occurrences causally related to treatment / all	2 / 2	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 46 (2.17%)	2 / 61 (3.28%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 46 (2.17%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			

subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysema			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Blood creatinine increased			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arterial restenosis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 46 (4.35%)	3 / 61 (4.92%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	4 / 4	7 / 7	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Atrial fibrillation			
subjects affected / exposed	3 / 46 (6.52%)	1 / 61 (1.64%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	5 / 5	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	2 / 46 (4.35%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block right			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			

subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiomyopathy			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 46 (2.17%)	1 / 61 (1.64%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 46 (0.00%)	2 / 61 (3.28%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 46 (2.17%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 46 (2.17%)	2 / 61 (3.28%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal lymphadenopathy			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Keratoconus			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendiceal mucocoele			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Oesophageal fistula			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal polyp			

subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 46 (4.35%)	1 / 61 (1.64%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	2 / 2	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 46 (2.17%)	2 / 61 (3.28%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 46 (0.00%)	2 / 61 (3.28%)	3 / 49 (6.12%)
occurrences causally related to treatment / all	0 / 0	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia pneumococcal			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomembranous colitis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 46 (0.00%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	0 / 46 (0.00%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic disorder			

subjects affected / exposed	1 / 46 (2.17%)	0 / 61 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Bosutinib, Accelerated Phase CML	Bosutinib, Philadelphia Chromosome Negative CML	Bosutinib: Chronic Myelogenous Leukemia
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	3 / 3 (100.00%)	69 / 163 (42.33%)
number of deaths (all causes)	0	2	19
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaplastic large-cell lymphoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Brain neoplasm			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Lymphoma			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pancreatic carcinoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			

subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	4 / 163 (2.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst ruptured			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	7 / 163 (4.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arterial restenosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal fracture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	6 / 163 (3.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	12 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	5 / 163 (3.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	7 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	4 / 163 (2.45%)
occurrences causally related to treatment / all	0 / 0	2 / 2	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block right			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiomyopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Keratoconus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendiceal mucocoele			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Oesophageal fistula			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal polyp			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			

Skin ulcer			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	4 / 163 (2.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic kidney disease			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	3 / 163 (1.84%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	5 / 163 (3.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	2 / 163 (1.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomembranous colitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid retention			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Bosutinib, Chronic Phase 2nd Line CML	Bosutinib, Chronic Phase 3rd Line CML	Bosutinib, Chronic Phase 4th Line CML
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 46 (100.00%)	61 / 61 (100.00%)	48 / 49 (97.96%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 46 (8.70%)	1 / 61 (1.64%)	8 / 49 (16.33%)
occurrences (all)	5	2	9
Haematoma			
subjects affected / exposed	0 / 46 (0.00%)	4 / 61 (6.56%)	1 / 49 (2.04%)
occurrences (all)	0	8	1
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	10 / 46 (21.74%)	15 / 61 (24.59%)	19 / 49 (38.78%)
occurrences (all)	13	18	29
Asthenia			
subjects affected / exposed	20 / 46 (43.48%)	9 / 61 (14.75%)	6 / 49 (12.24%)
occurrences (all)	32	12	8
Pyrexia			
subjects affected / exposed	7 / 46 (15.22%)	11 / 61 (18.03%)	13 / 49 (26.53%)
occurrences (all)	9	21	19
Oedema peripheral			
subjects affected / exposed	9 / 46 (19.57%)	11 / 61 (18.03%)	9 / 49 (18.37%)
occurrences (all)	16	29	18
Chest pain			
subjects affected / exposed	4 / 46 (8.70%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences (all)	5	1	0
Influenza like illness			
subjects affected / exposed	4 / 46 (8.70%)	1 / 61 (1.64%)	1 / 49 (2.04%)
occurrences (all)	5	1	2
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	9 / 46 (19.57%)	17 / 61 (27.87%)	12 / 49 (24.49%)
occurrences (all)	16	43	18
Cough			
subjects affected / exposed	8 / 46 (17.39%)	18 / 61 (29.51%)	3 / 49 (6.12%)
occurrences (all)	11	23	3
Pleural effusion			
subjects affected / exposed	6 / 46 (13.04%)	13 / 61 (21.31%)	9 / 49 (18.37%)
occurrences (all)	7	21	11
Oropharyngeal pain			
subjects affected / exposed	10 / 46 (21.74%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences (all)	10	1	0
Productive cough			
subjects affected / exposed	0 / 46 (0.00%)	4 / 61 (6.56%)	1 / 49 (2.04%)
occurrences (all)	0	8	1
Epistaxis			

subjects affected / exposed	3 / 46 (6.52%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences (all)	4	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 46 (8.70%)	2 / 61 (3.28%)	4 / 49 (8.16%)
occurrences (all)	5	2	4
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 46 (21.74%)	18 / 61 (29.51%)	16 / 49 (32.65%)
occurrences (all)	43	45	47
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 46 (19.57%)	11 / 61 (18.03%)	13 / 49 (26.53%)
occurrences (all)	30	16	32
Blood creatinine increased			
subjects affected / exposed	8 / 46 (17.39%)	7 / 61 (11.48%)	10 / 49 (20.41%)
occurrences (all)	12	22	18
Lipase increased			
subjects affected / exposed	9 / 46 (19.57%)	11 / 61 (18.03%)	5 / 49 (10.20%)
occurrences (all)	20	23	11
Amylase increased			
subjects affected / exposed	5 / 46 (10.87%)	8 / 61 (13.11%)	3 / 49 (6.12%)
occurrences (all)	8	11	7
Weight decreased			
subjects affected / exposed	2 / 46 (4.35%)	7 / 61 (11.48%)	4 / 49 (8.16%)
occurrences (all)	2	7	5
Gamma-glutamyl transferase increased			
subjects affected / exposed	3 / 46 (6.52%)	6 / 61 (9.84%)	3 / 49 (6.12%)
occurrences (all)	4	11	7
Blood uric acid increased			
subjects affected / exposed	1 / 46 (2.17%)	6 / 61 (9.84%)	2 / 49 (4.08%)
occurrences (all)	1	9	5
Blood folate decreased			
subjects affected / exposed	3 / 46 (6.52%)	2 / 61 (3.28%)	0 / 49 (0.00%)
occurrences (all)	3	3	0
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	2 / 46 (4.35%)	10 / 61 (16.39%)	3 / 49 (6.12%)
occurrences (all)	3	18	5
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 46 (8.70%)	2 / 61 (3.28%)	0 / 49 (0.00%)
occurrences (all)	5	2	0
Cardiac failure			
subjects affected / exposed	3 / 46 (6.52%)	2 / 61 (3.28%)	1 / 49 (2.04%)
occurrences (all)	3	2	2
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 46 (30.43%)	17 / 61 (27.87%)	14 / 49 (28.57%)
occurrences (all)	33	24	19
Paraesthesia			
subjects affected / exposed	3 / 46 (6.52%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences (all)	7	1	0
Dizziness			
subjects affected / exposed	8 / 46 (17.39%)	9 / 61 (14.75%)	9 / 49 (18.37%)
occurrences (all)	16	13	12
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 46 (15.22%)	14 / 61 (22.95%)	5 / 49 (10.20%)
occurrences (all)	15	37	9
Thrombocytopenia			
subjects affected / exposed	7 / 46 (15.22%)	6 / 61 (9.84%)	4 / 49 (8.16%)
occurrences (all)	33	18	24
Neutropenia			
subjects affected / exposed	3 / 46 (6.52%)	4 / 61 (6.56%)	0 / 49 (0.00%)
occurrences (all)	8	6	0
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 46 (6.52%)	1 / 61 (1.64%)	1 / 49 (2.04%)
occurrences (all)	7	1	1
Conjunctival hyperaemia			
subjects affected / exposed	3 / 46 (6.52%)	2 / 61 (3.28%)	0 / 49 (0.00%)
occurrences (all)	3	2	0

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	43 / 46 (93.48%)	54 / 61 (88.52%)	42 / 49 (85.71%)
occurrences (all)	129	131	106
Nausea			
subjects affected / exposed	15 / 46 (32.61%)	29 / 61 (47.54%)	25 / 49 (51.02%)
occurrences (all)	29	50	47
Vomiting			
subjects affected / exposed	13 / 46 (28.26%)	22 / 61 (36.07%)	19 / 49 (38.78%)
occurrences (all)	28	36	36
Abdominal pain			
subjects affected / exposed	14 / 46 (30.43%)	17 / 61 (27.87%)	16 / 49 (32.65%)
occurrences (all)	29	22	29
Abdominal pain upper			
subjects affected / exposed	19 / 46 (41.30%)	8 / 61 (13.11%)	9 / 49 (18.37%)
occurrences (all)	33	10	10
Constipation			
subjects affected / exposed	13 / 46 (28.26%)	11 / 61 (18.03%)	7 / 49 (14.29%)
occurrences (all)	14	15	8
Dyspepsia			
subjects affected / exposed	4 / 46 (8.70%)	6 / 61 (9.84%)	3 / 49 (6.12%)
occurrences (all)	7	7	3
Abdominal distension			
subjects affected / exposed	3 / 46 (6.52%)	5 / 61 (8.20%)	3 / 49 (6.12%)
occurrences (all)	4	7	3
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 46 (8.70%)	3 / 61 (4.92%)	2 / 49 (4.08%)
occurrences (all)	5	3	2
Flatulence			
subjects affected / exposed	5 / 46 (10.87%)	3 / 61 (4.92%)	1 / 49 (2.04%)
occurrences (all)	7	3	1
Abdominal discomfort			
subjects affected / exposed	3 / 46 (6.52%)	2 / 61 (3.28%)	1 / 49 (2.04%)
occurrences (all)	3	3	1
Gastrointestinal disorder			

subjects affected / exposed	3 / 46 (6.52%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences (all)	4	2	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	5 / 46 (10.87%)	6 / 61 (9.84%)	7 / 49 (14.29%)
occurrences (all)	6	9	10
Alopecia			
subjects affected / exposed	5 / 46 (10.87%)	5 / 61 (8.20%)	2 / 49 (4.08%)
occurrences (all)	5	5	2
Dry skin			
subjects affected / exposed	3 / 46 (6.52%)	3 / 61 (4.92%)	5 / 49 (10.20%)
occurrences (all)	4	4	5
Skin lesion			
subjects affected / exposed	4 / 46 (8.70%)	3 / 61 (4.92%)	2 / 49 (4.08%)
occurrences (all)	4	3	3
Erythema			
subjects affected / exposed	5 / 46 (10.87%)	2 / 61 (3.28%)	1 / 49 (2.04%)
occurrences (all)	5	4	1
Acne			
subjects affected / exposed	3 / 46 (6.52%)	3 / 61 (4.92%)	1 / 49 (2.04%)
occurrences (all)	3	3	1
Rash pruritic			
subjects affected / exposed	4 / 46 (8.70%)	3 / 61 (4.92%)	0 / 49 (0.00%)
occurrences (all)	7	4	0
Night sweats			
subjects affected / exposed	3 / 46 (6.52%)	0 / 61 (0.00%)	1 / 49 (2.04%)
occurrences (all)	4	0	1
Rash			
subjects affected / exposed	9 / 46 (19.57%)	8 / 61 (13.11%)	8 / 49 (16.33%)
occurrences (all)	16	16	12
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 46 (17.39%)	18 / 61 (29.51%)	10 / 49 (20.41%)
occurrences (all)	20	26	20
Myalgia			

subjects affected / exposed	7 / 46 (15.22%)	12 / 61 (19.67%)	4 / 49 (8.16%)
occurrences (all)	12	13	5
Pain in extremity			
subjects affected / exposed	8 / 46 (17.39%)	8 / 61 (13.11%)	5 / 49 (10.20%)
occurrences (all)	16	23	9
Bone pain			
subjects affected / exposed	5 / 46 (10.87%)	4 / 61 (6.56%)	3 / 49 (6.12%)
occurrences (all)	8	4	5
Neck pain			
subjects affected / exposed	4 / 46 (8.70%)	4 / 61 (6.56%)	2 / 49 (4.08%)
occurrences (all)	5	4	4
Intervertebral disc disorder			
subjects affected / exposed	3 / 46 (6.52%)	1 / 61 (1.64%)	1 / 49 (2.04%)
occurrences (all)	3	1	1
Back pain			
subjects affected / exposed	7 / 46 (15.22%)	13 / 61 (21.31%)	9 / 49 (18.37%)
occurrences (all)	10	13	14
Muscle spasms			
subjects affected / exposed	2 / 46 (4.35%)	5 / 61 (8.20%)	2 / 49 (4.08%)
occurrences (all)	2	7	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 46 (15.22%)	11 / 61 (18.03%)	8 / 49 (16.33%)
occurrences (all)	9	18	9
Influenza			
subjects affected / exposed	6 / 46 (13.04%)	3 / 61 (4.92%)	5 / 49 (10.20%)
occurrences (all)	9	4	8
Urinary tract infection			
subjects affected / exposed	1 / 46 (2.17%)	6 / 61 (9.84%)	2 / 49 (4.08%)
occurrences (all)	2	7	3
Bronchitis			
subjects affected / exposed	3 / 46 (6.52%)	3 / 61 (4.92%)	2 / 49 (4.08%)
occurrences (all)	5	5	2
Upper respiratory tract infection			
subjects affected / exposed	1 / 46 (2.17%)	5 / 61 (8.20%)	2 / 49 (4.08%)
occurrences (all)	1	6	2

Folliculitis			
subjects affected / exposed	6 / 46 (13.04%)	1 / 61 (1.64%)	0 / 49 (0.00%)
occurrences (all)	7	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 46 (8.70%)	10 / 61 (16.39%)	7 / 49 (14.29%)
occurrences (all)	5	15	13
Hyperuricaemia			
subjects affected / exposed	3 / 46 (6.52%)	0 / 61 (0.00%)	2 / 49 (4.08%)
occurrences (all)	4	0	3

Non-serious adverse events	Bosutinib, Accelerated Phase CML	Bosutinib, Philadelphia Chromosome Negative CML	Bosutinib: Chronic Myelogenous Leukemia
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	3 / 3 (100.00%)	162 / 163 (99.39%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	15 / 163 (9.20%)
occurrences (all)	1	1	18
Haematoma			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	5 / 163 (3.07%)
occurrences (all)	0	0	9
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	46 / 163 (28.22%)
occurrences (all)	1	1	62
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	36 / 163 (22.09%)
occurrences (all)	2	0	54
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	31 / 163 (19.02%)
occurrences (all)	0	0	49
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	29 / 163 (17.79%)
occurrences (all)	0	0	63
Chest pain			

subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	6 / 163 (3.68%)
occurrences (all)	0	1	7
Influenza like illness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	6 / 163 (3.68%)
occurrences (all)	0	0	8
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	39 / 163 (23.93%)
occurrences (all)	0	1	78
Cough			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	31 / 163 (19.02%)
occurrences (all)	1	1	39
Pleural effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	29 / 163 (17.79%)
occurrences (all)	0	1	40
Oropharyngeal pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	11 / 163 (6.75%)
occurrences (all)	0	0	11
Productive cough			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	5 / 163 (3.07%)
occurrences (all)	0	0	9
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	4 / 163 (2.45%)
occurrences (all)	0	0	5
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	11 / 163 (6.75%)
occurrences (all)	0	1	12
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	44 / 163 (26.99%)
occurrences (all)	0	0	135
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	33 / 163 (20.25%)
occurrences (all)	0	0	78
Blood creatinine increased			

subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	26 / 163 (15.95%)
occurrences (all)	1	0	53
Lipase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	25 / 163 (15.34%)
occurrences (all)	0	0	54
Amylase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	16 / 163 (9.82%)
occurrences (all)	0	0	26
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	14 / 163 (8.59%)
occurrences (all)	0	1	15
Gamma-glutamyl transferase increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	13 / 163 (7.98%)
occurrences (all)	0	1	23
Blood uric acid increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	9 / 163 (5.52%)
occurrences (all)	0	0	15
Blood folate decreased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	5 / 163 (3.07%)
occurrences (all)	0	0	6
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	15 / 163 (9.20%)
occurrences (all)	0	0	26
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	6 / 163 (3.68%)
occurrences (all)	0	0	7
Cardiac failure			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	6 / 163 (3.68%)
occurrences (all)	0	0	7
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 4 (50.00%)	0 / 3 (0.00%)	47 / 163 (28.83%)
occurrences (all)	2	0	78
Paraesthesia			

subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	5 / 163 (3.07%)
occurrences (all)	0	1	9
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	27 / 163 (16.56%)
occurrences (all)	0	2	43
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 3 (66.67%)	28 / 163 (17.18%)
occurrences (all)	0	5	66
Thrombocytopenia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	19 / 163 (11.66%)
occurrences (all)	2	2	79
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	7 / 163 (4.29%)
occurrences (all)	0	0	14
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	5 / 163 (3.07%)
occurrences (all)	0	0	9
Conjunctival hyperaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	5 / 163 (3.07%)
occurrences (all)	0	0	5
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 4 (100.00%)	2 / 3 (66.67%)	145 / 163 (88.96%)
occurrences (all)	7	3	376
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	70 / 163 (42.94%)
occurrences (all)	1	0	127
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	55 / 163 (33.74%)
occurrences (all)	0	2	102
Abdominal pain			
subjects affected / exposed	2 / 4 (50.00%)	0 / 3 (0.00%)	49 / 163 (30.06%)
occurrences (all)	3	0	83
Abdominal pain upper			

subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	37 / 163 (22.70%)
occurrences (all)	0	1	54
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	32 / 163 (19.63%)
occurrences (all)	0	2	39
Dyspepsia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	14 / 163 (8.59%)
occurrences (all)	1	0	18
Abdominal distension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	11 / 163 (6.75%)
occurrences (all)	0	0	14
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	10 / 163 (6.13%)
occurrences (all)	1	0	11
Flatulence			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	9 / 163 (5.52%)
occurrences (all)	0	0	11
Abdominal discomfort			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	6 / 163 (3.68%)
occurrences (all)	0	0	7
Gastrointestinal disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	4 / 163 (2.45%)
occurrences (all)	0	0	6
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	18 / 163 (11.04%)
occurrences (all)	0	0	25
Alopecia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	13 / 163 (7.98%)
occurrences (all)	0	1	13
Dry skin			
subjects affected / exposed	2 / 4 (50.00%)	0 / 3 (0.00%)	13 / 163 (7.98%)
occurrences (all)	2	0	15
Skin lesion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	9 / 163 (5.52%)
occurrences (all)	0	0	10

Erythema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	8 / 163 (4.91%)
occurrences (all)	0	0	10
Acne			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	7 / 163 (4.29%)
occurrences (all)	0	0	17
Rash pruritic			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	7 / 163 (4.29%)
occurrences (all)	0	0	11
Night sweats			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	4 / 163 (2.45%)
occurrences (all)	0	0	5
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	25 / 163 (15.34%)
occurrences (all)	0	0	44
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	37 / 163 (22.70%)
occurrences (all)	0	2	68
Myalgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	23 / 163 (14.11%)
occurrences (all)	0	0	30
Pain in extremity			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	22 / 163 (13.50%)
occurrences (all)	0	2	50
Bone pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	13 / 163 (7.98%)
occurrences (all)	0	2	19
Neck pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	10 / 163 (6.13%)
occurrences (all)	0	0	13
Intervertebral disc disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	5 / 163 (3.07%)
occurrences (all)	0	0	5
Back pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	29 / 163 (17.79%)
occurrences (all)	0	0	37
Muscle spasms			
subjects affected / exposed	0 / 4 (0.00%)	2 / 3 (66.67%)	11 / 163 (6.75%)
occurrences (all)	0	2	13
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	26 / 163 (15.95%)
occurrences (all)	0	0	36
Influenza			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	14 / 163 (8.59%)
occurrences (all)	0	0	21
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	9 / 163 (5.52%)
occurrences (all)	0	0	12
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	8 / 163 (4.91%)
occurrences (all)	0	0	12
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	8 / 163 (4.91%)
occurrences (all)	0	0	9
Folliculitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	7 / 163 (4.29%)
occurrences (all)	0	0	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 4 (25.00%)	1 / 3 (33.33%)	23 / 163 (14.11%)
occurrences (all)	1	1	35
Hyperuricaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	5 / 163 (3.07%)
occurrences (all)	0	0	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2017	Updated to add new secondary endpoints composed of duration of CCyR, duration of MMR and clarifications regarding the analysis of the primary endpoint. Decreased the number of subjects in the 4th-/later-line cohort from the initial target of 75 to at least 45 subjects. Removed the requirement of karyotype imaging submission for independent central review. Updated to provide scientific rationale regarding the inclusion of the Ph- CML subjects. Dose modification guidelines updated to align with clinical practice. Disease progression criteria updated according to the CML disease phase.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported